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Patentanmeldung Nr. | Patent application No. | Demande de brevet n°

03078277.5

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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DSM IP Assets B.V.
Het Overloon 1
6411 TE Heerlen
PAYS-BAS

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(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
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Process for the preparation of alkynols

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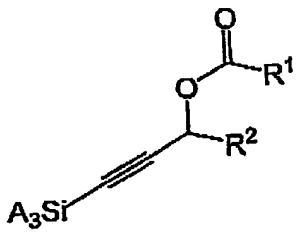
PROCESS FOR THE PREPARATION OF ALKYNOLS

The invention relates to a process for the preparation of an alkynol with formula $HC{\equiv}C\text{-}C(OH)\text{-}R^2$ (formula 2) wherein R^2 represents methyl, halomethyl or ethyl, wherein the corresponding protected alkynol with formula 1



(1)

wherein R^1 represents H, or an alkyl, alkenyl or aryl group, R^2 is as defined above and A_3Si represents a trisubstituted silyl group wherein each A independently represents an alkyl or an aryl group, in the presence of water and at least an equivalent amount of amine functionalities is converted into the alkynol with formula 2

Deprotection of the protected alkynols with formula 1, wherein both the protecting silyl group and the protecting acyl group are removed are known to be performed, for instance, in methanol in the presence of a base. A disadvantage of this method is that due to equilibrium considerations diluted systems with high amounts of methanol are required. Moreover due to small differences in boiling points between the reaction system and the alkynol, isolation via distillation is rather difficult.

Applicant now has developed a simple, one pot deprotection method which can be applied at high concentrations and which leads to virtually quantitative deprotection and high isolated yields of the desired alkynol, and wherein the desired product can easily be separated from the other reaction products.

The deprotection according to the invention is performed in the presence of water. The amount of water preferably is at least 0.4 equivalents calculated with respect to the amount of protected alkynol to be deprotected, most preferably at least 0.5 equivalents. If distillation forms (part of) the purification process, the amount of water preferably is less than 5 equivalents, most preferably less than 3 equivalents. In this case large amounts of water are disadvantageous in that they have to be removed before distillation of the alkynol with formula 2. Moreover if water forms

an azeotrope with the alkynol, water has to be removed by drying or any other physical or chemical method that is compatible with the system. Preferably less than 3, more preferably less than 1 equivalent of water calculated with respect to the amount of protected alkynol, is used in the deprotection step. Particularly advantageous is the use of 0.4 – 0.6 equivalents of water relative to the amount of protected alkynol with formula 1.

Suitable primary or secondary amines that can be used in the process of the present invention are, for instance, amines with 1-40 C atoms, including of course also for instance diamines and polyamines etc., amino alcohols, including any compound with one or more, for instance 1-20 (primary or secondary) amino groups and one or more, for instance 1-20 hydroxy groups, for instance amino alcohols having one amino group and one hydroxy group, in particular aminoethanol; amino diols, for instance diethanol amine; amino polyols; diamino glycols; polyamino polyols; aminothiols, including any compound with one or more, for instance 1-20 (primary or secondary) amino groups and one or more, for instance 1-20 SH groups, for instance amino thiols having one amino group and one SH group; amino thiols, for instance cysteine and derivatives thereof, amino poly thiols or polyamino polythiols. Accordingly, one molecule of the primary or secondary amine can contain more than 1 equivalent of amine functionalities. Preferably a primary amine or an amino alcohol, more preferably an aminodiol, particularly diethanolamine is used.

The amount of primary or secondary amine to be used may vary within wide limits. Preferably the amount used is less then 5 equivalents of amine functionalities, more preferably less than 2 equivalents calculated with respect to the amount of protected alkynol with formula 1. Most preferably the primary or secondary amine is used in an amount between 1 and 2 equivalents of amine functionalities, calculated with respect to the amount of protected alkynol.

The deprotection method according to the invention preferably is catalyzed by an amount of a base. Suitable bases that can be used are, for instance, (earth) alkaline metal (bi)carbonates, (earth) alkaline metal hydroxides, alkoxides and phenoxides. Preferably an (earth) alkaline metal carbonate, bicarbonate or hydroxide is used as the base. The basic functionality of the primary or secondary amine can of course also be applied as the base. The amount of base to be used may range within wide limits and may vary from catalytic amounts, for instance ≥ 0.01 equivalents calculated with respect to the amount of protected alkynol, up to 5, preferably up to 2 equivalents in a non-catalytic mode. In case distillation forms part of the purification,

the preferred amount of base may depend on the boiling point of the base. If the difference in boiling points of the base and the alkynol with formula 2 is smaller than 45 °C, preferably a catalytic amount of base, for instance 0.01-0.1 equivalents, is used.

The temperature at which the deprotection is performed is not critical and lies for instance between –10 and 150 °C, preferably between 10 and 100 °C, most preferably between 30 and 80 °C. The deprotection according to the invention may if desired be performed in the presence of a solvent in order to enhance the solubility of the various reacting agents. If no solvent is used in the deprotection, preferably the reagents are chosen such that the reaction system is as homogeneous as possible. Preferably no solvent is used as the process appears to be most efficient without the use of a solvent. Suitable solvents that may be used are for instance inert solvents having a high boiling point, for instance a boiling point of 200°C or more, for example dibenzylether.

After the deprotection step the reaction mixture, which may be homogeneous or may consist of 2 or more phases, may be subjected to purification. The purification may consist of one or more steps, preferably at least one of these steps is a distillation step. Before or after the distillation of the alkynol with formula 2, the purification may comprise for instance one or more extractions, filtrations, phase separations or distillations, if any.

In a particularly advantageous embodiment of the process according to the invention wherein purification is (partly) achieved by a distillation step, the reaction components are chosen such that the reagents present in the mixture subjected to distillation – optionally after one or more purification steps – have a boiling point which differs at least 45 °C, preferably at least 55 °C, from the boiling point of the alkynol with formula 2; alternatively, if the said boiling point difference is lower, less than stoichiometric amounts (for example, $\leq$ 10 mol.% compared to the amount of alkynol with formula 2) are present in the medium to be distilled. Preferably the phase containing the alkynol with formula 2 which is subjected to distillation contains the lowest possible amount of water and/or compounds having a boiling point which differs less than 45 °C from the boiling point of the alkynol with formula 2. Preferably this amount of water is less than 3 equivalents calculated with respect to the amount of alkynol with formula 2.

The phase containing the alkynol with formula 2 which is subjected to distillation, preferably contains less than 10 mol.% calculated with respect to the amount of alkynol with formula 2, of each component of which the difference in boiling

point compared to the boiling point of the alkynol with formula 2 is less than 45 °C.

The deprotection according to the invention can be performed starting from any protected alkynol of formula (1) wherein R^1 represents H, an alkyl group with for instance 1-20 C-atoms, preferably 1-6 C-atoms, an alkenyl group with for instance 2-20 C-atoms, preferably 2-6 C-atoms, or an (hetero) aryl group optionally containing one or more O or N atoms, with for instance 4-20 C-atoms, preferably 5-10 C-atoms; A_3Si represents a trisubstituted silyl group wherein each A independently represents an alkyl group with for instance 1-20 C-atoms or an aryl group, for instance a phenyl group, and R^2 represents methyl, halomethyl, wherein halo represents F, Cl, Br or I, or ethyl. The alkyl, alkenyl and aryl groups of R^1 or A may contain any substituents that are inert in the reaction system. Suitable substituents are, for example, alkyl groups, aryl groups, alkoxy groups, alkenyl groups, dialkylamino groups, halogens, nitrile, nitro, acyl, carboxyl, carbamoyl or sulphonate groups which may contain for instance 0-10 C-atoms. The (protected) alkynols may be in an enantiomerically enriched form, for instance with an ee > 80%, preferably > 90%, most preferably > 95%, in particular > 99%. An alkynol with formula 2 that particularly advantageously can be prepared with the process according to the invention is 3-butyn-2-ol or its enantiomers, in particular (R)- or (S)-3-butyn-2-ol starting from an ester of (R)- or (S)-4-trialkylsilyl-3-butyn-2-ol, for instance an ester of (R)- or (S)-4-trialkylsilyl-3-butyn-2-ol and a carboxylic acid or a mono ester of (R)- or (S)-4-trialkylsilyl-3-butyn-2-ol and succinic acid.

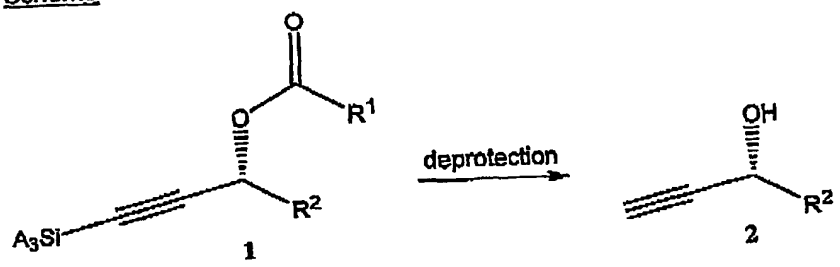
The starting material of the deprotection, the ester of (R)- or (S)-4-trialkylsilyl-3-butyn-2-ol, may, for instance, be prepared via (enzymatic) resolution, for instance by (enzymatic) stereoselective acylation, wherein a mixture of (S)- respectively (R)-4-trialkylsilyl-3-butyn-2-ol and the ester of (R)- respectively (S)-4-trialkylsilyl-3-butyn-2-ol is obtained, followed by separation of the (R)- respectively (S)-4-trialkylsilyl-3-butyn-2-ol ester and the (S)- respectively (R)-4-trialkylsilyl-3-butyn-2-ol in the mixture, for instance by converting (S)- respectively (R)-4-trialkylsilyl-3-butyn-2-ol to a high boiling or water soluble ester for instance a succinic ester with a suitable acylating agent, for instance succinic anhydride, and a suitable catalyst, for instance dimethylamino pyridine.

The invention will further be elucidated by the following examples, without however be restricted thereby.

Deprotection trialkylsilyl esters (1)

Deprotection examples are illustrated in scheme below.

Scheme

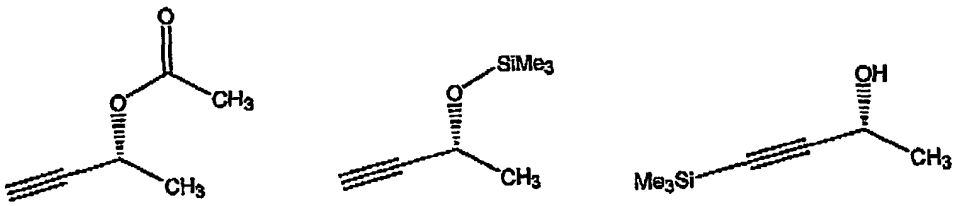


1a A = $R^1 = R^2 = Me$
1a' A = $R^2 = Me$, $R^1 = -(CH_2)_2COOH$

2a $R^2 = Me$
2b $R^2 = Et$
2c $R^2 = -CH\ Cl$

The deprotection reaction and side products are monitored by GC analysis using a CP-Sil 5 CB column (program: 3 minutes at 50°C, 15°C/min → 250°C, 5 minutes at 250°C)

Side products



Example I

Deprotection using n-butylamine

A 5 ml vial containing a magnetic stirring bar was charged with (R)-4-trimethylsilyl-3-butyn-2-yl acetate (**1a**) (1 mmol), K_2CO_3 (0,1 mmol) and n-butylamine (2.4 mmol). Reaction vial was sealed with a teflon-lined cap and the temperature of the reaction mixture was increased to 80°C. After 3 hours, water (1.2 mmol) was added to the reaction mixture. Reaction was continued for 1 night giving **2a** in 97% yield. Starting

material **1a** was not completely converted. **1a** and **5a** stayed behind in the reaction mixture in respectively 1 and 3 % assay yield.

Example II

Deprotection using amino alcohols

A 5 ml vial containing a magnetic stirring bar was charged with (R)-4-trimethylsilyl-3-butyn-2-yl acetate (**1a**) (1 mmol), K_2CO_3 (0,1 mmol) and amino alcohol. Reaction vial was sealed with a teflon-lined cap and the temperature of the reaction mixture was increased to 80°C. At given reaction time (table 1), water was introduced in the reaction mixture. Reaction was continued overnight at 80°C. Deprotection results are summarized in table 1.

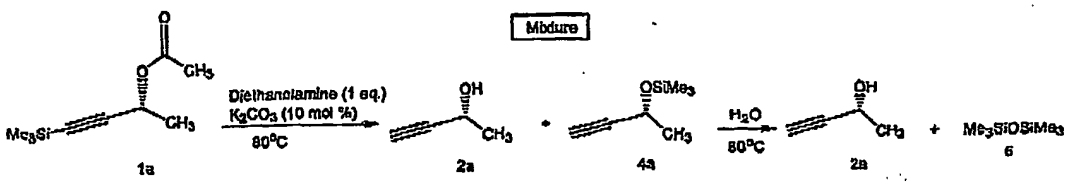
Table 1 Deprotection of **1a** using amino alcohols

Exp	Amino alcohol	H_2O			Yield[b] (%)				
		(eq.)	(mmol)	t (h)[a]	**2a**	**3a**	**4a**	**5a**	**1a**
1	2-amino-1-butanol	1.2	1.2	3	>99		< 1		
2	Diethanolamine	1.2	0.6	0	99		1		
3	Diethanolamine	1.2	1.6	0	98		2		
4	Diethanolamine	1.2	1.2	3	> 99				
5	Diethanolamine	1.2	0.6	4	> 99				

a) reaction time before the addition of water b) determined by GC using the "corrected 100 % method".

Example III

Deprotection (R)-4-trimethylsilyl-3-butyn-2-yl acetate (**1a**) and isolation of (R)-3-butyn-2-ol by distillation



A 500 ml round bottom flask was charged with (R)-4-trimethylsilyl-3-butyn-2-yl acetate (**1a**) (68.41 g, ~0.37 mol), diethanolamine (41.0 g, 0.39 mol) and K_2CO_3 (5.1 g, 0.037 mol). The reaction mixture was stirred at 80°C for 1.5 hours. In first part of the deprotection, (R)-4-trimethylsilyl-3-butyn-2-yl acetate was completely converted to a mixture of (R)-3-butyn-2-ol and (R)-O-TMS-butynol (**4a**). In second part, the remaining (R)-O-TMS-butynol (**4a**) was converted to (R)-3-butyn-2-ol by the addition of H_2O (4 g, 0.22 mol). The reaction was continued for 2 h at 80°C in order to achieve complete conversion.

Upon standing, the reaction mixture separated into two liquid layers. One layer is predominantly TMS-ether **6** and second layer exists of a solution of (R)-3-butyn-2-ol in the remaining reaction matrix.

Distillation

The two-phase reaction mixture was distilled directly after deprotection by slow increase of temperature to 120°C. In first fraction, an azeotropic mixture of TMS-ether **6** and (R)-3-butyn-2-ol (**2a**) came over, which separated in the receiver into two liquid layers. At this point, (R)-3-butyn-2-ol (**2a**) was separated in high purity from TMS-ether **6**. Distillation of the remaining (R)-3-butyn-2-ol was continued at 120°C by slow decrease of the pressure to approximately 800 mbar. When distillation was almost finished the pressure was further decreased in order to distill residual amounts of (R)-3-butyn-2-ol. The combined distillation fractions (product separated from **6** in first fraction and product collected in second fraction) yielded 24.1 g (0.34 mol) (R)-3-butyn-2-ol.

For further purification, the collected (R)-3-butyn-2-ol fractions were distilled at atmospheric pressure at an oil bath temperature of 125°C. (R)-3-butyn-2-ol (18.0 g, 0.26 mol) was smoothly distilled at a bottom temperature of 108 – 110°C. Quantitative analysis by GC using an external standard method showed a high degree of purity.

Example IV

Deprotection using 1,2-diaminoethane

A 5 ml vial containing a magnetic stirring bar was charged with (R)-4-trimethylsilyl-3-butyn-2-yl acetate (**1a**) (1 mmol), dihexylether as internal standard (0.1 mmol), H_2O, K_2CO_3 and 1,2-diaminoethane (1.2 mmol). Reaction vial was sealed with a teflon-lined cap and the temperature of the reaction mixture was increased to 80°C.

Deprotection was continued for 16 h at given temperature.

For analysis, reaction mixture was diluted with 1 ml dichloromethane. GC-sample was prepared by dissolving 50 µl of vigorous stirring reaction mixture in 1 ml CH_2Cl_2. The results are summarized in table 4

Table 4 Deprotection **1a** using 1,2-diaminoethane

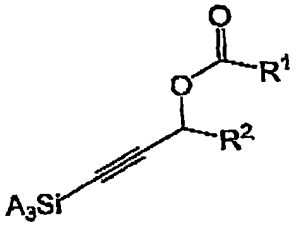
Exp	K_2CO_3	H_2O	Yield[a] (%)				
	(mmol)	(mmol)	**2a**	**3a**	**4a**	**5a**	**1a**
1[b]			33		2	53	12
2		1,6	99		1		
3	0.1	1,6	100				

a) Assay yield determined by GC using dihexyl ether as internal standard

b) Comparative experiment

CLAIMS

1. Process for the preparation of an alkynol with formula $HC{\equiv}C\text{-}C(OH)\text{-}R^2$ (formula 2) wherein R^2 represents methyl, halomethyl or ethyl, wherein the corresponding protected alkynol with formula 1



(1)

wherein R^1 represents H, or an alkyl, alkenyl or aryl group, R^2 is as defined above and A_3Si represents a trisubstituted silyl group wherein each A independently represents an alkyl or an aryl group, in the presence of water and at least an equivalent amount of amine functionalities is converted into the alkynol with formula 2.

2. Process according to claim 1 wherein the amount of water is between 0.5 and 3 equivalents calculated with respect to the amount of protected alkynol with formula 1.

3. Process according to claim 1 or 2 wherein in addition a base is present.

4. Process according to claim 3, wherein the base is an (earth) alkaline metal carbonate, an (earth) alkaline metal bicarbonate or an (earth) alkaline metal hydroxide.

5. Process according to any one of claims 1-4, wherein the amount of amine functionalities is between 1 and 2 amine equivalents calculated with respect to the amount of alkynol with formula 1.

6. Process according to any one of claims 1-5, wherein R^2=methyl.

7. Process according to any one of claims 1-6, wherein subsequently the reaction mixture is subjected to at least one purification step of which at least one step is a distillation step.

8. Process according to claim 7, wherein the phase containing the alkynol with formula 2 which is subjected to distillation (i) contains less than 3 equivalents calculated with respect to the amount of alkynol with formula 2 of water and (ii) contains less than 10 mol.% calculated with respect to the amount of alkynol with formula 2, of each component of which the difference in boiling point

compared to the boiling point of the alkynol with formula 2 is less than 45 °C.

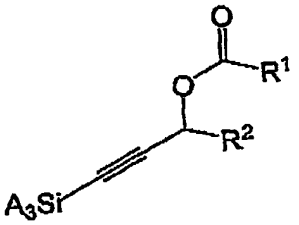
9. Process according to anyone of claims 1-8, wherein the protected alkynol is enantiomerically enriched.

10. Process according to claim 9, wherein first the enantiomerically enriched protected alkynol with formula 1 is prepared via enzymatic resolution of the mixture of enantiomers of the corresponding silyl-protected alkynol followed by isolation of the enantiomerically enriched protected alkynol with formula 1, and subsequently the enantiomerically enriched protected alkynol with formula 1 is subjected to a process according to claim 8 or 9.

11. Process according to claim 10, wherein the enzymatic resolution is performed via stereoselective acylation of the mixture of enantiomers of the silyl-protected alkynol, followed by conversion of the remaining enantiomerically enriched enantiomer of the silyl-protected alkynol to a high boiling or water soluble ester.

ABSTRACT

Process for the preparation of an alkynol with formula HC≡C-C(OH)-R^2 (formula 2) wherein R^2 represents methyl, halomethyl or ethyl, wherein the corresponding protected alkynol with formula 1



(1)

wherein R^1 represents H, or an alkyl, alkenyl or aryl group, R^2 is as defined above and A_3Si represents a trisubstituted silyl group wherein each A independently represents an alkyl or an aryl group, in the presence of water and at least an equivalent amount of amine functionalities is converted into the alkynol with formula

Preferably, the amount of water is between 0.5 and 3 equivalents calculated with respect to the amount of protected alkynol with formula 1.

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